Division of Cardio-Renal Drug Products
Medical Officer Review

NDA 21-272
Remodulin ™ (treprostinol sodium) Injection

This review covers the submissions dated 12 April 2001 and 15 May 2001. This review incorporates Dr. Lawrence, the FDA statistician's review for the April 12 submission. United Therapeutics submitted these two submissions in response to a meeting on 11 April 2001. At that meeting United Therapeutics proposed to analyze the combination of six-minute walk and the Borg-dyspnea score by combining these metrics into a single value. The rationale for combining these two parameters is they are the least likely (but not totally) devoid of bias due to unblinding by the nearly universal presence of infusion site pain limited to those treated with UT-15. Placebo-treated subjects rarely had infusion site pain.

United Therapeutics also submits additional data on the use of narcotic pain medication among those in treated long-term with UT-15.

Lastly, the sponsor submits information on a total of eight patients who were transitioned to UT-15 after adverse events while receiving Flolan infusions.

1) Additional analyses combining six-minute walk and Borg-dyspnea Index

The sponsor's analysis was <u>not</u> pre-specified and only considered after the results of the study were available. The overall process of defining a metric was to combine normalized (to a scale of 0-1) rankings of six minute walk and normalized (to a scale of 0-1) ranking of the Borg-dyspnea scale. The resultant values were summed and then the subjects were then re-ranked with the ranks normalized (on a scale of 0-1). The sponsor graphs the % of patients in each group who achieve at least a given rank versus the rank scale that spanned the range of 0 to 1.

The sponsor treats dropouts in different ways. Two extremes of these analyses are shown below. The first analysis (Figure 1) treated those who died, were transplanted, discontinued due to worsening of disease or who were too ill to perform the assessment as worse outcomes. All others who discontinued had last observations carried forward. Since there were far more discontinuations in among those treated with UT-15 than among those treated with placebo, additional analyses that assigned worse rank to subjects who discontinued based on criteria such as death or transplantation during the 100 days since randomization even after discontinuation due to adverse events. Other analyses also treated those who received flolan during the first month or those who received flolan during the 100 day span of the study as worst case scenarios. The analysis shown as Figure 2 treats all subjects who discontinued as worst outcomes independent of the reason for discontinuation and is the most conservative of the analyses performed by the sponsor. [Comment: The most conservative analysis would treat he UT-15 as worst outcome and censor placebo patients.]

Based on these two analyses, there was a difference among those treated by placebo and those treated with UT-15. The interpretation of these curves however is obscure. Perhaps the only interpretation is that approximately 57-60% of those treated with UT-15 did better than the median (rank of 0.5) than the 43-40% of those treated with placebo. Describing this benefit in words is not easy and would require de-convoluting the ranks. In essence all that can be said is that there is little benefit in walk distance (< 10 meters) and some benefit in Borg-dyspnea measurements.

This interpretation adds little to the information currently available.

The very small p-values associated with this analysis is hardly surprising. As Dr. Lawrence notes in his review

> " [W]hen the p-value from one variable is very small and this variable is combined with a second variable, it should not be surprising that the p-value from the sum of the two variables is small".

One last point, the Borg-dyspnea measurement is not entirely devoid of the problem of unblinding. The methodology that was employed by the sponsor was however, about a s good as it gets. There was a designated individual who not involved in the subject's care elicited this metric. Unblinding, however, may have occurred at the level of the subject-investigator. The investigator likely knew the subject's treatment based on the presence or absence of infusion site pain.

Again combining the six-minute walk with the Borg index does not really add much to what we know about the individual components.

Figure Addendum- 1 Combined Rank analysis with patients who discontinued due to death, transplantation, worsening of status or unable to exercise at week 12 treated as worst outcomes

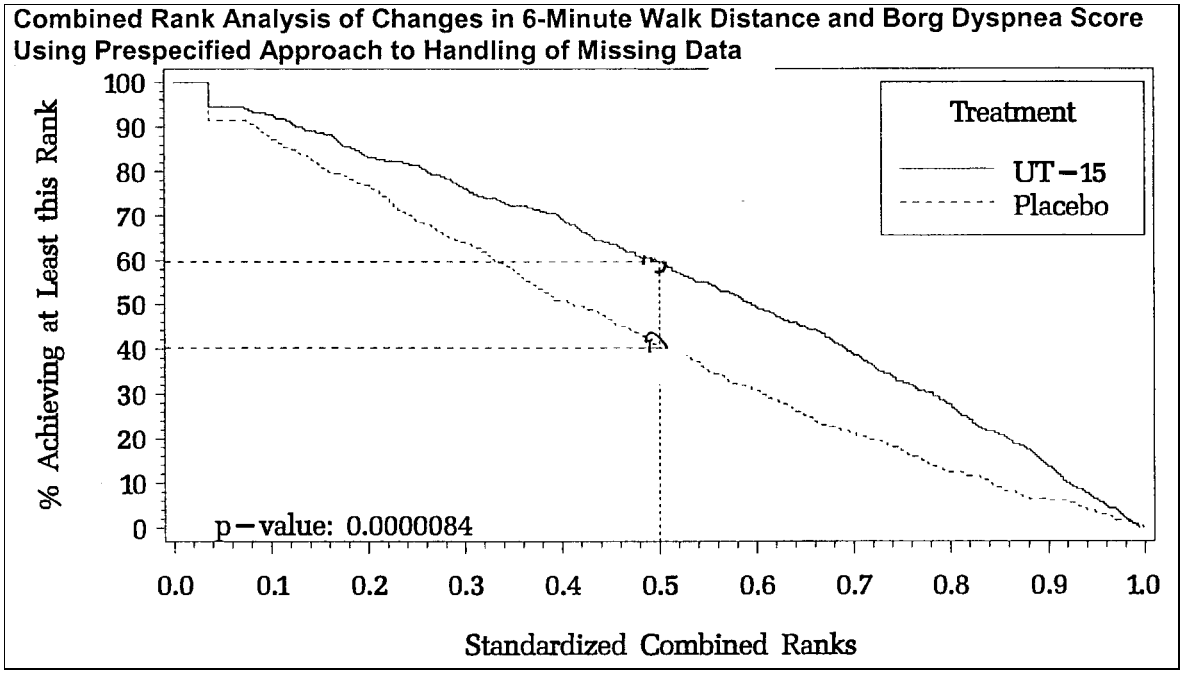
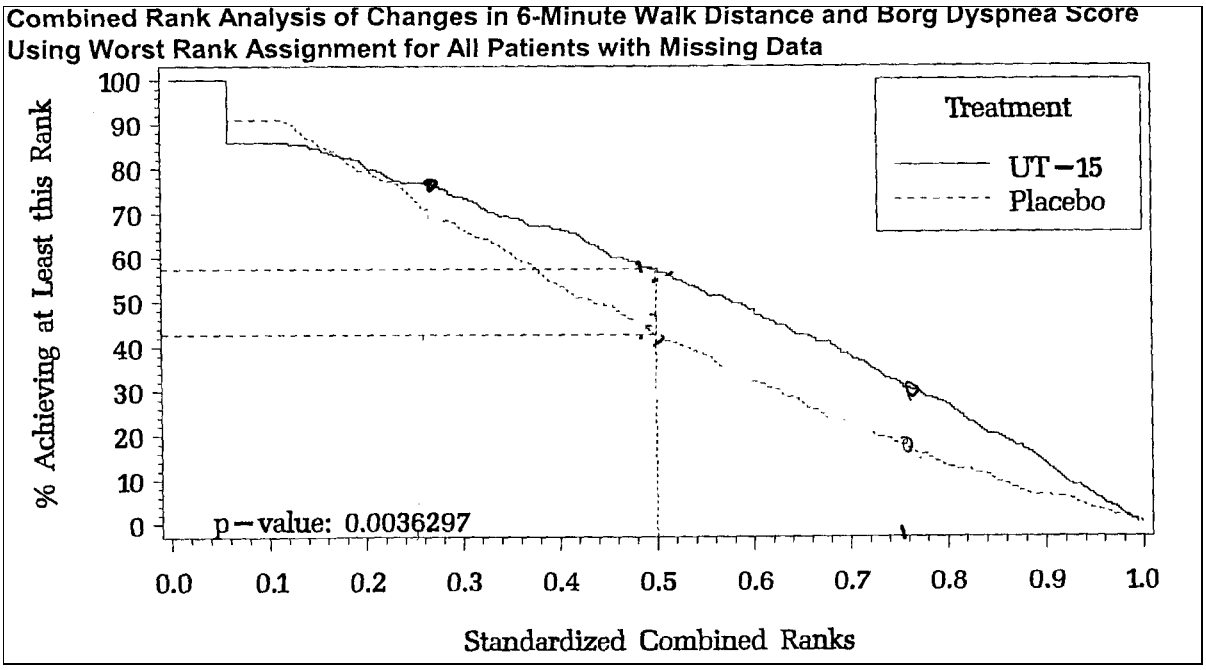


Figure Addendum- 2. All dropouts treated as worst outcomes



2) Use of Narcotics.

The sponsor submits several analyses as to the use of narcotics (of all types) among those who were treated with UT-15 and had infusion-site pain. The sponsor notes that 27% of those enrolled were treated with opiates during the two pivotal studies P01: 04 and P01: 05. Of these patients 19% were treated with either class II narcotics (that includes codeine, oxycodone, methadone, meperidine or fentanyl) or Class III narcotics (that include codeine mixtures, dihydrocodeine or hydrocodone).

Among those who were enrolled into study P01: 06, 135/631 (21%) of the subjects were treated with narcotics. Those who entered P01: 06 were those who enrolled into previous studies and completed these studies on UT-15 (i.e. did not dropout or die and therefore tolerated the UT-15 infusion) or placebo patients who completed crossed over to UT-15. In addition, there were 208 subjects who were enrolled into this open-label extension who were naïve to either infusion.

During study P01:06 , subjects who were prescribed narcotics were not asked whether the pain medication was necessary on an on-going basis and whether the pain was still present. These prescriptions were left for the patient to fill use on a PRN basis.

In order to ascertain some measurement of the need for narcotics, 535 of the 545 subjects still on treatment were contacted as to whether they were using narcotics the day prior to contact. Of those contacted 45 (8%) were taking some form of opiate.

[Comment: The on-going need for narcotics such be interpreted in the context that the duration of inquiry was short (1 day), the population who were questioned were those who did not discontinue due to site pain and did not include those whose pain was sufficiently severe to require NSAIDS.]

3) Cross-over subjects from Flolan to UT-15

No protocol was submitted. The data that was reviewed consists of 12 pages of study summary.

As of May 1, 2001, eight subjects (6 males and 2 females) age range 29-54 with pulmonary hypertension were transitioned from intravenous flolan to subcutaneous UT-15. Some specifics are shown below.

Table addendum-1 specifics among those switched from Flolan to UT-15

Patient #	Reason for Flolan D/C	Time on Flolan (months)	Dose of Flolan	UT-15 dose after transition (ng/kg/min)	Time of Transition	Time on UT-15 (months)
1102001	Recurrent paradoxical emboli	5	3.5	3	24	15
1121001	Central line infection	29	26	15	50	5
1121002	Jaw/leg pain Line infection	36	75	65	120	3
1129001	Line infection-septicemia	26	22.5	23.3	42	2
1129002	Line infection-epidermal necrosis	33	40	36.6	54	2
1153001	Line infection	21	15	7	36	9
1153002	Severe Headache, jaw pain and diarrhea	30	13	10	22	6
1153003	Line infection-septicemia	19	18	16	22	6

The sponsor notes no increase in pulmonary hypertension symptoms during the transition period. The sponsor also notes that adverse events were those of prostacyclin excess and/or infusion site discomfort. In addition, one patient # 1102001 had a cerebrovascular accident during the transition period from Flolan o UT-15. Seven of the eight subjects are reported by the sponsor to be still alive and doing well. One subject is reported as having worsening symptoms while on Flolan that continued after transition to UT-15.

Comment: There was no randomization process to determine whether those transitioned actually benefited from Flolan (i.e. worsening of symptoms upon decrease of dose of flolan). No efficacy conclusions can be derived from this data.

Abraham Karkowsky, M.D. Ph.D. _____

Cc: HFD-110 A Karkowsky
N Stockbridge
D Throckmorton
E Fromm